

**Remarks**

Claims 1-20 and 28-29 were pending prior to this Response. By the present communication, claim 28 has been amended; claim 29 has been canceled without prejudice or disclaimer; and new claims 30-35 have been added. Claims 21-27 were previously canceled. The amendments and new claims do not raise any issues of new matter being supported by the specification and claims as filed. Subsequent to the entry of the present amendment, claims 1-20, 28, and 30-35 are pending and at issue. Reconsideration of the application is respectfully requested in view of the following remarks.

Applicants note that the Office Action states that claims 1-20 are pending. In a discussion with the Examiner on September 17, 2007, the Examiner stated that claims 28 and 29 are also pending in the present application and rejected on the same grounds as claims 1-20.

**Rejections under 35 U.S.C. §103**

The Examiner maintains the rejection of claims 1-20 under 35 U.S.C. 103(a) over Debendetti et al. (US patent no 6,063,910) in view of Merrified et al. (WO 00/37169). As discussed above, in a discussion with the Examiner on September 17, 2007, the Examiner stated that claims 28 and 29 are also currently pending in the application and that these claims are also rejected under 35 U.S.C. 103(a). Applicants have canceled claim 29 rendering the rejection moot as to the canceled claim. Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom.

The recent U.S. Supreme Court decision in *KSR International v. Teleflex Inc.* (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the

general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The Examiner has identified the following issues in relation to the claim rejections:

- (i) notwithstanding our response in the previous Office Action that the prior art does not disclose the use of an aqueous solvent, the Examiner alleges that “the prior art clearly establishes the use of such aqueous solvent”. Further, the Examiner alleges that the Applicant has not qualified “what is precisely meant by the term “aqueous solvent”; and
- (ii) notwithstanding our response in the previous Office Action that there is no reasonable expectation of success in combining the references, the Examiner alleges that “absolute predictability is not required to establish obviousness”.

Applicants will address each issue in turn.

#### **I. Aqueous Solvent**

Applicants submit that the meaning of the term “aqueous solvent” is one that would be well known to one of ordinary skill in the art. In addition, Applicants submit that one of ordinary skill in the art would give meaning to the term in its context. The term is not intended to have a special meaning in the present application.

By way of support, the following online dictionaries define “aqueous solvent” and “aqueous solution” to be (see Exhibit A, submitted herewith):

| Online dictionary         | Term             | Definition   |
|---------------------------|------------------|--|
| The Free Dictionary       | aqueous solution | A solution in water (see Appendix A)   |
| Chemical Terms Dictionary | aqueous          | Literally, watery. Used to described solutions of substances dissolved in water (see Appendix B) |
| MSDS                      | aqueous          | A solution in water. A more exact  |

|                         |         |  |
|-------------------------|---------|--|
| Hyperglossary           |         | definition is a solution in which the solute (the substance dissolved) initially is a liquid or a solid and the solvent is water (see Appendix C). |
| About.com:<br>Chemistry | solvent | the component of a solution that is present in the greatest amount. It is the substance in which the solute is dissolved (see Appendix D)          |

Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because the cited combination fails to teach or suggest all of the recited claim limitations. Applicants submit that neither Debendetti nor Merrified discloses the use of an aqueous solvent within the scope of the standard definition of the term. Debendetti discusses “a solution of water and ethanol” at column 6, lines 28-29, but, as would be known by one of ordinary skill in the art, such a phrase would mean, in its context, that water is dissolved in the ethanol, the ethanol being the solvent which is present in a greater amount than the water. Such a solution is not an aqueous solution and would not be regarded as such by one of ordinary skill in the art. This is illustrated by the two examples in Debendetti using 90% ethanol and 10% water, again, not an aqueous solution as the major component of the solution is ethanol, not water.

The Examiner has also pointed out claim 5 of Debendetti, which claims the solvent for the protein being “aqueous ethanol”. Given the disclosure of Debendetti as a whole, and the interpretation that would be put on the document, in its context, by one of ordinary skill in the art, Applicants consider that for claim 5 to have support in the body of the Debendetti specification, “aqueous ethanol” must mean ethanol containing water, i.e., water dissolved in a solvent of ethanol. This is also consistent with the examples and the natural meaning of the term.

In addition, Applicants consider that Debendetti teaches away from the present invention, as it states at column 6, lines 29 to 32 that:

A solution of water and ethanol has been used. However, the presence of water in such solution has been found to lower production of small particle protein.

Thus, Debendetti indicates that the presence of water in the solution compromises the yield of small particles of proteins. In teaching away from the use of water in the process, Debendetti provides no motivation to one of ordinary skill in the art to either modify the process of Debendetti or to combine Debendetti with Merrified to arrive at the invention of the pending claims. In relation to this point, Merrified states on page 6, lines 18 to 21 that:

Suitable solvents, especially for dissolution of the material, include organic solvents such as C<sub>1-5</sub> alkyl, C<sub>1-5</sub> alkanooate esters such as ethylacetate, C<sub>1-5</sub> alcohols such as methanol, and di C<sub>1-5</sub> alkyl ketones such as acetone, water and mixtures thereof, such as an alcohol-ketone mixture such as a methanol-acetone mixture.

Moreover, the examples in Merrified do not involve use of water as a solvent to any extent. Merrified does not therefore suggest or motivate the use of aqueous solutions. Given that Debendetti clearly teaches away from the use of an aqueous solvent, there is no motivation or suggestion for one of ordinary skill in the art to combine the teachings of Debendetti and Merrified to arrive at the invention claimed in the present application.

In relation to claims 28 and 29, the Examiner stated in the previous Office Action that in Debendetti "the resulting particles may then be collected on the suitable collection means" (see column 5, lines 19 to 22). Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness because there is no motivation or suggestion to combine the references. This passage in Debendetti does not refer to a second collection vessel as required by pending claim 28. Merrified allegedly makes reference to the particles being collected by a cyclone or a filter, however, as discussed above, given that Debendetti clearly teaches away from

the use of an aqueous solvent, there is no motivation or suggestion for one of ordinary skill in the art to combine the teachings of Debendetti and Merrified to arrive at the invention claimed in the present application. Accordingly, Applicants submit that the pending claims, as amended, are not obvious over Debendetti in view of Merrified.

Additionally, as outlined in the specification of the present application at page 10, lines 1-2, an unexpected and surprising advantage of the subject invention is:

The ability to use aqueous solutions thereby enabling concentrated solutions of material to be processed with minimal risk of deactivation of biological activity.

In the process of the present invention, contact with organic solvents is minimized, limited only to the time that the solution of the substance (an aqueous solution) mixes with the dense gas. In this way, the potential for protein denaturing is minimized.

## **II. Predictability**

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because the combination does not suggest a reasonable expectation of success. The Examiner alleges that "absolute predictability is not required to establish obviousness". The Examiner further alleges that only a reasonable expectation of success is needed. Applicants respectfully disagree with the Examiner's determination of what is "reasonable" and assert that one of ordinary skill in the art would not have sufficient knowledge to have a reasonable amount of predictability in determining the effects in altering the parameters of such precipitation processes. Applicants direct the Examiner to the declaration of one of ordinary skill in the art, Dr. Linda Sze Tu, submitted herewith as Exhibit B, that discusses the lack of predictability of such dense gas process.

In light of Dr. Sze Tu's declaration, for the Examiner to suggest that one of ordinary skill in the art could read Debendetti and be motivated to combine it with disparate aspects of Merrified and have a reasonable expectation of arriving at the claimed process simply does not correlate with the literature examples described in the declaration. Applicants respectfully

submit that the Examiner has failed to recognize the large amount of effort that one of ordinary skill in the art would have to perform to develop such a dense gas process, notwithstanding the high level of knowledge held by one of ordinary skill in the art.

Dr. Sze Tu's declaration discusses a number of references from the scientific literature which show that it is difficult to predict the effects of changes made to dense gas processes. As discussed in the declaration, one study, reported by Ting et al. (submitted herewith as Exhibit C), showed that the solubility of the organic compound naproxen varied non-linearly at higher cosolvent concentration. Hutchenson and Foster (submitted herewith as Exhibit D) stated that predicting SCF behavior was difficult in "even the simplest of systems" and that the difficulty was even more pronounced in more complex systems. The study reported by Jouyban et al. (submitted herewith as Exhibit E) found that correlating experimental results with model systems provides varying levels of predictability in supercritical CO<sub>2</sub> systems. Dr. Sze Tu concludes that it is difficult for one of ordinary skill in the art to predict the outcome of one change to a dense gas process, and simultaneously introducing a second change in the process would make the outcome almost impossible for one of ordinary skill in the art to predict.

Accordingly, Applicants submit that the claimed invention is not obvious over Debendetti in light of Merrified and respectfully request that the rejection of claims 1-20 and 28 under 35 U.S.C. §103(a) be withdrawn.

In re Application of:  
Foster et al.  
Application No.: 10/017,135  
Filed: December 7, 2001  
Page 12

PATENT  
Atty Docket No.: HILLS1100

**Conclusion**

In summary, for the reasons set forth herein, Applicants submit that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge \$405.00 as payment for the Request for Continued Examination fee for small entity to Deposit Account No.: 07-1896. The Commissioner is also authorized to charge any additional fees required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: October 25, 2007



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